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CADMIUM, CARCINOGEN, CO-CARCINOGEN AND ANTI CARCINOGEN

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ABSTRACT

As a stress agent, inducing apoptosis and blocking it, Cd can have both helpful and harmful effects. The atmosphere is a thin envelope which makes the world a global village. Cd is the most toxic metal in air. As both the first and second messenger of the stress response, it is synergistically toxic with all other stressors, including many other carcinogens. Elimination of Pb and its replacement with added benzene in gasoline appears to have increased the toxicity of atmospheric Cd. With scientific understanding of the molecular basis of Cd's role in carcinogenesis and anti-carcinogenesis, primary cancer prevention can be practiced by reducing Cd and chemical air pollution and educating the public on smoke cessation, healthy eating habits and stress reduction. Using the existing information on Cd and its effects, determinations could be made on established cancers so that individualized treatment protocols can be developed to improve patient care.

KEY WORDS : Cadmium, Carcinogen, Co-carcinogen, Anti-carcinogen.

INTRODUCTION

The toxic potential of cadmium became obvious with its increasing industrial use at the beginning of the 20th Century. Due to its extraordinarily long biological half life, cadmium tends to accumulate in the body. Exposure to cadmium fumes results in cadmium intoxication. The Itai Itai disease was observed in Japan, the result of eating cadmium contaminated rice. Cadmium has been recognized as a dangerous environmental contaminant, which may lead to carcinogenesis. The world wide production of cadmium is 12,000 to 15000 tons/year. Fifty to sixty percent of the product is used for galvanization. Roughly, 10% is used in pigments . Furthemore, cadmium is used as a stabilizer in plastics and is used in radiation screens and batteries. Cadmium is now a ubiquitous pollutant present in tobacco smoke, incineration fumes, phosphate fertilizers and sewage sludge. With an increase in global population there is an increase in Cd air pollution. In Japan the level of Cd in human kidneys has increased from 43.95 to 73.47 mg/g in the last decade in spite of a drop of Cd levels in food supplies (1). Teenagers have levels approaching those of adults. A recent study (2) reported Cd levels of 5-160 mg/g in the kidneys of penguins living in Antarctica. Lichen studies done in Europe indicate that Cd is the only metal increasing in air. All these studies support the conclusion that Cd air pollution is an increasing global problem.

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Cd increases free radicals, promotes lipid peroxidation, and depletes anti-oxidants (3) and is carcinogenic. Cd affects ion transport through membranes (4), energy availability through mitochondrial function (5), detoxification through microsomal enzymes , intercellular communications by affecting cell adhesion in epithelial cells , and many cell signalling functions by affecting intracellular calcium , inositol polyphosphate, and protein kinase C (6).

Absorption, metabolism and excretion

Of all the metals Cd is the most easily absorbed and the most influenced by nutritional factors. It has a special affinity for multiple sulfhydryl groups, but it binds weakly to so many other compounds, that it moves to all compartments of the cell. Very low Cd

concentrations down to 100 pM stimulate cell growth and DNA synthesis significantly (7).

Cadmium is characterized by a very long biological half-life (10-30 years). Humans are exposed to cadmium mainly via contaminated food. Cadmium air concentrations (1to 5 ng/m^3) and increases to 40ng/m^3 in a few highly industrialized towns, do not contribute substantially to the total body burden in most areas. A remarkable inhalative uptake may be observed during occupational exposure to cadmium dust or aerosols. Cadmium containing particles may be retained in the alveoli. Animal experiments suggest that 50% or more of inhaled cadmium is absorbed from the respiratory tract. The absorption rate of cadmium from the respiratory tract into the plasma is determined by the particle size and water solubility of the inhaled particles.

Cadmium ions bind to the calcium binding protein in the intestinal mucosa and therefore, a low Ca concentration in food, enhances cadmium absorption. Cadmium absorption is increased 4-5 fold in animals and humans with iron deficiency. Investigations of transfer kinetics show that the Michaelis Menten constant is increased without changing Vmax. Therefore, it may be assumed that cadmium may share the intestinal transport mechanism for iron. The intestinal absorption of cadmium has 2 steps: (i) Cadmium ions are bound to the apical membrane of the mucosal cells of the small intestine. This process is fast, saturable and can be inhibited by calcium ions. (ii)The absorption from the mucosal cells into the plasma determines, the rate of cadmium absorption.

Interactions

Cd has complex interactions with metals, chemicals and hormones. Cd is antagonized by Zn and is synergistically toxic with copper (Cu), tin (Sn), and nickel(Ni). Both antagonism and synergism were found with mercury (Hg) and Cd depending on the concentration. A combined administration of Ni and Cd produced fibrosarcomas in female rats (8). Cadmium interacts with various chemicals and the toxicity of these chemicals is influenced by a variety of factors which affect the co-toxic agent Cadmium . Toxic substances such as dioxins, pesticides and herbicides bind to the estrogen receptor. Estrogen increases the uptake of Cadmium into the liver, kidneys and mamary glands. Since Cadmium binds to the steroid binding site of DNA, it can be expected, that Cd will have a modulatory role on steroid mediated cellular processes (9).

Effect of cadmium on metallothionein

Metallothionein is a cysteine rich protein that is expressed in large amounts when excess quantities of certain metal ions, including toxic ones such as Cd^{2+} or Pb^{2+}, are present in cells. Metallothionein thus serves a protective role and may also be involved in the control of metal transport, storage, and concentration under more normal conditions. In metallothionein, nearly 30-35% of the amino acids of this class of small proteins are cysteine residues, the sulfhydryl groups of which bind avidly to soft metal ions , such as Cd^{2+}, Hg^{2+}, Pb^{2+}. One of the biological functions of this protein is to protect cells against the toxic effects of these metal ions. With exposure to Cd, organisms or cells increase their production of metallothionein (MT). Cd moves from the cell membrane to the nucleus where it binds to DNA, inducing gene transcription in as little as 4 hours . In Cd resistant cells the transcription of MT can increase 20-40 fold. in humans there are at least 14 genes that have been identified which control the production of MT (10).

Cd and Zn are physiologic antagonists. A Zn-dependent metal responsive element that induces MT-IIA gene does not respond to Cd at any dose. Moreover, C-myc, which is induced by Cd , represses Zn promoted isoforms of MT but not Cd or dexamethasone induced isoforms . Cd binds to a metal responsive element in the MT-I promoter, activating it in Cd exposed and non-Cd exposed cells , suggesting that Cd plays a role in all stress responses, not just those caused by Cd exposure. Because it gets into cells readily, it can modulate any stress response (11). If all goes well, Cd detoxifies itself. With Cd's ability to enter the cell through many channels and to affect many cell reactions that occur

with stress responses, it is reasonable to consider Cd both a first and second messenger for the stress response that is highly conserved in nature. The induction of MT to bind free Cd is one of the ways to terminate the stress response so that the cell can return to normal housekeeping function. (Fig. 1.)

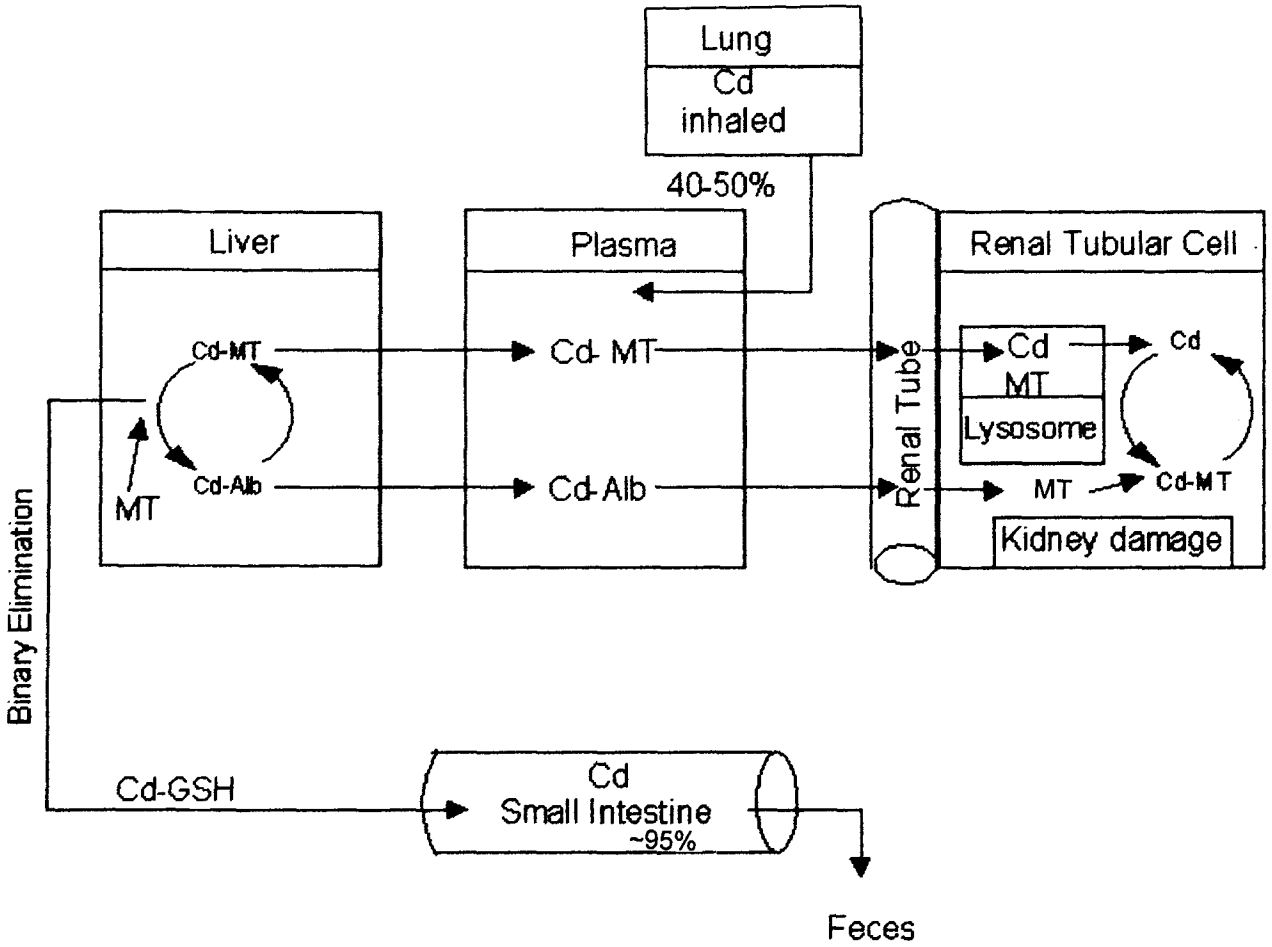

Fig. 1. Absorption, distribution, metabolism and excretion of cadmium. After absorption from the small intestine (~5%) or lung (40-50% Cd is bound to albumin (Alb) and taken up into hepatocytes. Within hepatocytes, cadmium stimulates the synthesis of metallothionein that binds cadmium. Biliary excretion of glutathion-bound cadmium is of minor importance. Cd-metallothionein is released from hepatocytes into plasma. From plasma Cd-metallothionein is transported to renal tubules via glomerular filtration. A small fraction is excreted with urine. The major part is reabosorbed by the tubular cells. In lysosmes Cd-metallothionein is metabolized. Cd is released and induces metallothioneim synthesis again. When a critical Cd concentration is exceeded (>200 mg/kg) in the renal cortex, kidney damage cannot be excluded.

Carcinogenesis

Carcinogenic doses of Cd induce oxidative stress while impairing cellular defense mechanisms against such stress. With Cd-induced testicular cancer, 12 hours after exposure to Cd lipid peroxidation, iron (Fe) content, and cellular production were elevated in testicular Leydig cells (12, 13). It is evident that co-exposure to a variety of chemicals results in this carcinogenic state.

By altering cell metabolism, Cd fosters cell proliferation. In cell culture systems, this effect can be blocked by equimolar concentrations of Se. The cell surface receptor activated by Cd (6), interacts with oncogenes. Cd is known to increase the expression of two oncogenes, C-myc and C-jun . C-

myc is associated with aggressive tumors. Cd also alters the tumor suppressor protein p53, eliminating its suppressant effect on cancers in a variety of tumors (14). In any stress situation which results in a loss of tight epithelial junctions, either in the GI tract or in the vasculature, Cd is taken up by these lining cells and the transfer of nutrients is inhibited, compromising the cellular defenses. Moreover, Cd effects on the primary tumor may allow shedding of tumor cells into the blood and the breaks in the vascular lining allow metastatic cells access to tissue. Cd has effects on proteases which are necessary for basement-membrane degradation and invasion of tumor cells(15,16). Air pollution with Cd can make cancers resistant to cancer treatments. Tumors resistant to radiation and chemotherapy are resistant to Cd and may contain an overexpression of the MT gene. Overexpression of MT in primary invasive ductal carcinoma of the breast is associated with metastases which are resistant to anti-cancer drugs and radiation and have a poor prognosis. Increased metallothionein concentration is found in human small cell lung cancer cells resistant to cisplatin and CdC12 (17). It is possible that the resistance blocks apoptosis.

Over-expression of heat shock protein 60 in ovarian cancer is associated with resistance to cis-platin therapy and a poor prognosis. Researchers did not find an induction by Cd but they evaluated the cells at 4 hours. It was found that induction by Cd of this protein was maximal at 18 hours after exposure. Over-expression of heme-oxygenase in human lung adenocarcinoma cell line (CL3R) is associated with resistance to Cd, arsenite, and adriamycin (18). Heme-oxygenase is induced by oxidant stress and Cd in conditions of low glutathione. Glutathione suppresses the induction of heme oxygenase (19).

Effects on cathepsin D

There have been several studies on the effects of Cd on cathepsin D, an important acid protease in lysosomes. Cd increases cathepsin D mRNA in human breast cancer cells. Over-expression of Cathepsin-D, by transfection increased metastases from rat tumor cells. Elevated levels of cathepsin D were found in breast secretions from women with breast cancer . In human ovarian carcinoma cell lines, I nM 17-beta-estradiol increases secretion of procathepsin D by 50% , an effect blocked by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). An inhibitory effect of TCDD on estrogen stimulated formation of lactate from glucose in human breast cancer cells was reversed by a phorbol ester, an effect that could involve Cd but that was not addressed in the study. The increased incidence of reproductive tumors in fish and humans around pollution sources of Cd and dioxins suggests a synergistic effect (20).

Anti-carcinogenesis

Although Cd can be carcinogenic, especially in combination with other chemicals, it can induce apoptosis. Apoptosis, is programmed cell death, associated with stress proteins. Apoptosis is normal during embryogenesis and rids the body of stressed, infected, and cancerous cells. Apoptosis occurs in cells with a fluid membrane which facilitates Cd uptake, with increased intracellular calcium, an effect of Cd on the Ca ATPase (4), and a change in the expression of c-fos and c-myc , Cd effects (11). Mammalian cells contain a $Ca^{(2+)}$-dependent endonuclease which is a necessary step in apoptosis. Zn inhibits this process, depending on the free Ca^{2+} concentration. It appears that a balance between Zn and Ca regulates this process . Cd alone stimulates the endonuclease, replacing Ca^{2+}, and is more inhibitory than Zn in blocking apoptosis. This ability to take the place of both Zn and Ca and to have higher potencies than either ion, helps explain the highly divergent effects that it can produce(21-23).

As a stress agent Cd can both initiate and kill chemically or spontaneously initiated cancers of the lung, liver, and blood in rats (24). Lung tumors induced by certain chemical exposures in humans are inhibited in individuals who are heavy smokers. Unfortunately, smokers generally suffer from other toxic effects from Cd exposure.

Female cancers

With the reduction in atmospheric Pb, which antagonizes the effects of Cd, and the increase in environmental chemicals that bind to the estrogen

receptor, combined with Cd pollution, one can predict a change in female morbidity and mortality. The increase in breast cancer could be in response to Cd. Infiltrating inflammatory cells in the stroma appear to be the source of cathespin D levels associated with enhanced metastatic potential of node negative cancers, an effect that Cd could promote. Cd induces human mononuclear cells to produce large amounts of interleukin-8, which is the cytokine causing neutrophil infiltration (25). Cathepsin D stimulates the release of transforming growth factor-alpha (TGF-alpha), which stimulates breast cell growth by binding to TGF-alpha/epidermal growth factor receptors on the cell surface . Metastases from human breast tumor cells grown in mice without estrogen supplementation, are associated with elevated cell production of cathepsin D (26).

The behavior of dioxins is particularly problematic. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) acts as liver tumor promoter in female rats but not male rats . In the human breast cancer cell line MCF-7, TCDD acts as an anti-estrogen but when combined with a phorbol ester the anti-estrogen response is inhibited . In areas in Maine and Florida, contaminated with herbicides there are increased reproductive tumors in clams and increased human mortality rates due to ovarian cancer (27). The herbicides are contaminated with TCDD and air pollution with Cd would act as a co-carcinogen.

Tamoxifen, an anti-estrogen commonly used in breast cancer therapy, although non-toxic when administered alone, in conjunction with administration of TCDD caused a centrilobular pattern of hepatocellular degeneration and necrosis with perivascular infiltration of inflammatory cells in female GDI mice. A co-toxic effect with ambient Cd pollution could explain this dramatic effect on toxicity. A protective effect by lipoic acid, which blocks Cd-induced hepato-toxicity (28) would support the hypothesis of Cd involvement. Such complex interactions are also seen with dehydro-epiandrosterone (DHEA) which inhibits growth of mammary cancer cells in intact rats but stimulates it in ovariectomized, estrogen deficient animals. This has led to the hypothesis that low DHEA increases mammary carcinoma risk in premenopausal women . Cd is taken up more readily by the female adrenal than the male. It has inhibitory effects on basal and ACTH-stimulated steroidogenesis. With stress and pollution producing lower levels of DHEA, increased breast cancer could result in premenopausal women and those receiving hormone replacement therapy. Chronic cervicitis and cervical cancer are increased in smokers (29) and associated with human papilloma virus. It is likely that Cd facilitates the carcinogenic effects of the virus which it does with murine retrovirus infections.

Male tumors

Prostate cancer has been associated with increased Cd levels in the soil in Spain. It is one of the cancers that has been increasing in incidence and severity. Older patients in Utah with aggressive tumors had a higher intake of dietary fat , a source of added pesticides. Cd exposure from occupational exposure, high dietary intake, or smoking increased the risk for aggressive prostate tumors . Men employed as janitors had greatly increased risk for aggressive tumors in this study. The carcinogen 3,2*-dimethyl-4-aminobiphenyl when combined with Cd produced significantly more prostate carcinomas in rats than either chemical given alone, showing a synergistic effect (30). Janitors are exposed to Cd in dust and other toxic chemicals in cleaning supplies. Experimentally Cd can produce testicular and prostate cancers in rodents (12,13,15,16).

Lung, bladder and colon cancer

Synergy of Cd with other carcinogenic chemicals undoubtedly plays a role in the development of lung cancer in smokers and non-smokers exposed to passive smoke. The effects of such synergy have been studied in rats using Cd, n-nitrosohepta-methyleneimine, (NHMI) and asbestos fibers to produce lung cancer (31). Elevated levels of Cd, Ni and Cr are found in lung cancer and colorectal cancer and the metal levels are correlated with blood levels of tumor markers (32).

Workers exposed to 4-aminobiphenyl, which is a potent bladder carcinogen, who developed chloracne

from exposure to dioxin (TCDD) in 1949, had increased mortality from soft tissue sarcoma, bladder cancer and respiratory cancer (33). It is likely that Cd could be a co-carcinogen with dioxin and 4-aminobiphenyl.

Clinical evaluation of Cd exposure and toxicity

1. In most instances, one can find evidences for Cd exposure from environmental sources and active and passive smoke exposure. Urinary-cotinine is correlated with blood Cd . Co-exposure to physical, emotional, chemical, or biological stressors, nutritional deficiencies, exaggerated responses to stress with psycho-neuro-endo-immune alterations, and genetic susceptibility are factors that suggest increased levels of free Cd. There is a wide variability in sensitivity to the toxicity of Cd ions (34).

2. Free Cd is not measured by blood, urine and hair Cd levels. Mag-fura-2 can be used to measure free Cd levels in cells. The Cd concentration in blood collected at autopsy is several hundred times higher than values measured before death(35). Formalin fixative greatly reduces the level of Cd found in tissues (36).

3. By exposing dispersed cancer cells to varying concentrations of Cd and evaluating their viability in 24 hours, it should be possible to identify Cd sensitivity or resistance before the administration of radiation or chemotherapy, which might aggravate the condition of patients with resistant tumors. Cd effects on gene expression, such as over-expression of the MT gene, heat shock protein 60, or heme oxygenase can be used to identify Cd resistance in cancer cells using immunological stains.

4. Decreased anti-oxidants, lipid peroxidation, elevation of lactate dehydrogenase, alkaline, phosphatase, eosinophilia, lymphopenia, elevated monocytes, fever, cachexia, viral, bacterial and fungal infection, neurotoxicity, fatigue, and muscle weakness are non-specific effects of increased free Cd.

Therapeutics

1. Cd could be used therapeutically in cancer treatments to induce apoptosis in Cd sensitive tumor cells. Anti-sense oligonucleotides complimentary to the messenger RNA coding for MT-II increase the sensitivity of neuroblastoma cells to Cd (37).

2. Anti-fungal herbs have anti-carcinogenic effects and chelate and remove Cd, ie garlic, Pau D'Arco, and licorice.

3. High doses of vitamin C eliminate plasmids in bacteria which confer cadmium resistance. It is conceivable that high doses of vitamin C could make cancer cells Cd sensitive as well.

4. Cd can be used therapeutically in gene therapy to incorporate plasmids and promote gene expression. These attributes could be used in new gene therapies to restore the very malfunctions it may have caused.

5. Mg and Zn protect normal cells from toxic effects of chemotherapeutic agents which may occur in conjunction with released Cd. Niacin as NAD^+, protects DNA from oxidative strand breaks (38), so a deficiency would have a cancer promoting effect. Zn deficiency prevents the mobilization of vitamin A, another cancer fighting vitamin from the liver.

6. N-acetyl-cysteine facilitates Cd excretion, increases intracellular glutathione, and prevents the production of interleukin-8 induced by Cd, as does EDTA, a metal chelator (25).

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